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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAOUD, CHRISTINE J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,517	EATON ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/6/05, 7/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5 are pending in the instant application and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 06 June 2005 have been fully considered but are not deemed persuasive.

Specification

Applicant's submission of a substitute specification is noted. As was provided in the previous office action:

> 37 CFR § 1.125 Substitute specification.
>
> (c) **A substitute specification submitted under this section must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text**. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. **The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. An accompanying clean version (without markings) must also be supplied.** Numbering the paragraphs of the specification of record is not considered a change that must be shown pursuant to this paragraph.

The substitute specification filed 06 June 2005 has not been entered because it does not conform to 37 CFR 1.125 (c) because: a marked up copy showing the changes relative to the immediate prior version of the specification is not provided.

Claim Rejections - 35 USC §§ 101/112

Claims 1-5 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons of record in the previous Office action and for those reasons provided below.

Applicant argues at page 6 of the response that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently available" to the public in order to satisfy utility requirements. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining 'substantial' utility." (MPEP § 2170.01). The argument has been fully considered, but is not persuasive. That section of the MPEP also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101." For reasons discussed in the previous Office action, even if the encoding polynucleotide has utility, one cannot on that that basis alone support a utility for the encoded protein or antibody which binds the encoded protein because the prior art provides sufficient support to make a correlation between mRNA and encoded protein

level unpredictable. For example, Haynes et al. (of record in the instant application; Electrophoresis 19: 1862-1871, 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph, and Figure 1). Haynes et al. provide evidence that the polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (page 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. The results of Hu et al., J. Proteome Res. 2003, were discussed in previous Office action(s) and show that the correspondence between mRNA and protein levels cannot be assumed in cancerous tissue.

Applicant argues on pages 6-7 and 21 that *In re Brana* states that "Usefulness in patent law... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to administer to humans;" and that the USPTO has the initial burden of showing "that one of ordinary skill in the art would reasonably doubt the asserted utility." The argument has been fully considered, but is not persuasive. While *Brana* did deal with a rejection under 35 USC 112, first paragraph, the rejection was direct toward utility—specific, substantial and credible use—instead of enablement. While it is true that

administration of a pharmaceutical to a human is not always necessary for either utility or enablement, one must know how to use the invention without undue experimentation. The USPTO has met the burden of showing one skilled in the art would reasonably doubt the asserted utility by showing that the correspondence between mRNA and protein levels is not predictable and will be further discussed below.

Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention cannot be used. As to the nature of the invention, it is an antibody that "specifically binds" to a polypeptide encoded by a nucleic acid with no known specific association other than that asserted by Applicants of higher expression in normal lung compared to lung tumors. The polypeptide itself was not evaluated in the specification for actual expression in tissues. Since the encoding mRNA is expressed in lung tissue, one would reasonably expect the encoded protein also to be expressed, though at what levels it would be expressed are unknown. The protein does not have a recognized/characterized physiological/biochemical property. As to the state of the prior art, other encoding nucleic acids usable for tumor markers have been identified, though none of those identified as a tumor marker were identical or highly similar to SEQ ID NO:11. Therefore, the connection of SEQ ID NO:11 to normal tissue compared to tumors was not known. While the skill in the art for differential screening of nucleic acids has existed for over a decade, interpretation of the results depends, for example, on

relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given. There is very little guidance or direction about using the claimed invention except that the nucleic acid of SEQ ID NO:11 is more highly expressed in normal lung compared to lung tumor tissue. However, this disclosure does not convey to the claimed antibodies. The specification provides no information as to the specific type of tumor tested, no levels of expression are provided, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened is not disclosed. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

On pages 7-8, Applicant cites *Fujikawa v. Wattanasin* and *Cross* cases, arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure to support a specific and substantial or well established utility or to allow the skilled artisan to use the claimed invention without undue experimentation. Because, as previously discussed, there is

critical information lacking which includes: whether differences in nucleic acid expression of PRO300 were significant, under what conditions differences could be detected, what levels (relative or absolute) were detected in tumor and normal control, and whether protein levels correlate with nucleic acid levels, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention.

Applicant argues at page 9 and 19 of the response that the data presented in Example 18 are differential mRNA levels, not gene amplification. Applicant asserts that the Examiner "misinterpreted the data" and that Example 18 reports data regarding differential mRNA levels, not gene amplification data. Applicant argues that "whether gene amplification leads to increased gene expression is irrelevant to this particular application" and that "PRO300 mRNA is differentially expressed in certain tumors" and that it is irrelevant whether this is due to gene copy number or some other factor. Applicant's arguments are not persuasive because gene copy number would be relevant to the data provided in the instant specification. The art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy *before* the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, *pre-cancerous* lung epithelium is often aneuploid. See especially p. 4, Figure 4. Because aneuploid DNA can be found in normal tissue, detection of increased DNA copy number does not necessary mean those cells containing the DNA are cancerous. If the nucleic acid molecule being amplified by Applicant is from a gene with an increased copy number due to aneuploidy, then the results in the

instant specification are suspect because there has been no correction for aneuploidy. The comparison of "normal" lung to "tumor" lung must be corrected for events such as aneuploidy as well as the "normal" lung being corrected for environmental factors, such as smoking, which can affect lung epithelium and gene expression levels. Therefore, the data presented in the instant specification that PRO300 mRNA is greater in "normal" lung compared to lung tumor does not provide a specific and substantial utility for the claimed invention because this data does not support the use of the claimed antibodies as diagnostic probes for lung cancer based on the evidence provided. Furthermore, as the claims are directed to antibodies which bind the encoded polypeptide, and the specification provides no information on the expression of the encoded polypeptide, there is no evidence or data to suggest that the encoded polypeptide has any relation to lung cancer.

Applicants argue (pages 10-12) that one skilled in the art would be convinced there is a "significant probability" that the expression of the polypeptide will correlate with encoding nucleic acid expression or, put another way, one skilled in the art would not reasonably doubt the correlation. The argument has been fully considered, but is not persuasive. While one can find prior art that supports a "significant probability" that mRNA and protein levels will correlate, there is influential prior art of record that requires the Examiner maintain that, as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:11 positively correlates with the expression of the protein of SEQ ID NO:12. The advent of proteome analysis

has only recently begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. It is also noted that the information on which the assumption of a correlation between mRNA and protein levels was based came from findings in normal, noncancerous tissue. Indeed, there is evidence in the art to refute generalizations about gene/protein correlations even in normal tissue. For example, Haynes et al. (Electrophoresis 19 : 1862-187l , 1998) as discussed above showed from studies with yeast that among 80 proteins studied which were relatively homogenous in half-life and expression level, no strong correlation existed between protein and transcript levels. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph, and Figure 1). In a separate comparison by Fessler et al. (J. Biol. Chem. 277(35): 31291-302, Aug. 2002) examining lipopolysaccharide-activated neutrophils (col. 2, beginning of last paragraph on page 31300) it is stated, "Parallel use of DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other systems." Fessler et al. warn (first sentence page 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels." Chen et al. (cited by

Applicants, Mol. Cell Proteomics 1.4:304, 2002) studied 165 proteins from lung adenocarcinoa tumors expressed by 98 individual genes Their findings provide further evidence that one cannot assume the level of mRNA will correlate with the level of expressed protein for any given gene or any given protein (paragraph bridging pages 312-313):

> The results of this study indicate that the level of protein abundance in lung adenocarcinomas is associated with the corresponding levels of mRNA in 17% (28 proteins) of the total 165 protein spots examined. This was substantially higher than the amount predicated to result from chance alone (which was 5.1) and suggest that a transcriptional mechanism likely underlies the abundance of these proteins in lung adenocarcinomas. We also demonstrated that the expression of individual isoforms of the same protein may or may not correlate with the mRNA, indicated that the separate and likely post-translational mechanisms account for the regulation of isoform abundance. These mechanisms may also account for the differences in the correlation coefficients observed between stage I and stage III tumors, indicating that specific protein isoforms show regulatory changes during tumor progression.

Further, it was shown (page 309, col. 2, 5th line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression levels also showed up to a 28-fold variation in their mRNA levels." Chen showed that not only with mRNAs that encode a single protein but also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in

levels of expression with their encoded proteins. Given the unknown amount that mRNA copy number of PRO300 increased in normal lung compared to tumors, and the evidence provided by Haynes et al., Hu et al. (cited in the previous Office action), Fessler et al. and Chen et al., one skilled in the art would not have assumed that a small increase in mRNA copy number would correlate with significantly increased polypeptide levels. The level of increase of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO300 polypeptide levels were significantly decreased in the tumor samples in order to use antibodies in a diagnostic manner. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Note that the invention must have a specific and substantial utility at the time the application is filed. As stated above, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels

between normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form that can be used without necessary further experimentation.

Applicants argue (pages 11-12) that polypeptides such as PRO300 which are differentially expressed in certain cancers are useful as diagnostic tools. The argument has been fully considered, but is not persuasive. Were PRO300 differentially expressed and were this expression significant, repeatable and the information sufficiently complete to allow use of the polypeptide without undue experimentation, it would have utility as a diagnostic tool. It, however, has none of these necessities. There is no showing or reasonable expectation that PRO300 is differentially expressed in certain cancers, even though its encoding nucleic acid of SEQ ID NO:11 was more highly expressed in "normal lung" compared to lung tumor, though specifically which kind and at what levels is unknown.

Applicant (page 12) asserts that "the examiner has failed to offer relevant evidence to support her rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data" and that "given the well-estabilished correlation between a change in the level of mRNA with corresponding change in the levels of the encoded protein, the PRO 300 protein is likely differentially expressed in lung tumor". Applicant's statements are argumentative and factually incorrect. The Examiner has provided evidence in the form of peer-reviewed journal articles that demonstrate the dogma relied upon by Applicant

and the Declarants is not a law of nature. The evidence of record in the instant application support the holding that mRNA expression levels alone are not reliable predictor of protein expression levels. Therefore, one of ordinary skill in the art would not conclude that such would be the case in light of the prevailing art that teaches that this assumption should not be made because mRNA expression levels are not predictive of protein expression levels, absent evidence to the contrary.

Applicants argue (pages 12-13 and 15) that the data in Example 18 as discussed in the Declaration of Grimaldi (previously submitted as Exhibit 1) demonstrates at least a two-fold difference in expression between normal and tumor tissues and the usefulness of the encoding nucleic acid as a diagnostic tool for determining the presence or absence of a tumor. The argument has been fully considered, but is not persuasive. The conclusory statement of Grimaldi of the necessary existence of an at least two-fold differentiation in nucleic acid expression does not support a utility for or enable the invention because it does not fill important gaps in the disclosure needed to use the invention without significant further experimentation, such as expression level range for normal and tumor tissues, specific types of lung tumors detectable, and probability of detection for any particular lung tumor type (*e.g.*, whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested), or if and how much the PRO300 polypeptide is expressed in normal lung *versus* tumor. Even though the detection in Example 18 of the specification was carried out using cDNA libraries from tumor and corresponding normal tissue sample

and, according to the declaration, the libraries were made from pooled samples of tissues, this does not fill the above discussed gaps. It is noted that Grimaldi in paragraph 6 of the declaration describes the detection as "semi-quantitative" and the specification for Example 18 as "standard quantitative". The declaration also says (paragraph 5) that "Data from a pooled sample are more likely to be accurate than data from a single individual." This begs the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. Clinical diagnostics are not usually geared toward a populous but toward an individual's particular condition. While a "relative difference in expression between normal tissue and suspected cancerous tissue" can be informative, without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of lung tissue that can used, and other questions, the specification has not provided the invention in an enabling form. Therefore, the declaration would not be sufficient to overcome the rejections of the claims under 35 USC 101 or 112, first paragraph, for the reasons discussed above, were the declaration submitted in the instant application.

Applicants argue (page 14) that experimental details such as values of differences in transcript level are not necessary to establish utility of the claimed subject. The argument has been fully considered, but is not persuasive. The Office is not requiring anything. The specification has failings which the Examiner pointed out. While current availability of a claimed invention is not always necessary, the invention must still meet the requirements of 35 USC 101

and 112, first paragraph. 35 USC 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same ...." For the reasons discussed here and in previous Office actions, it is maintained the specification does not contain an enabling disclosure or provide a specific and substantial credible utility or a well established utility, and the declarations submitted as evidence from co-pending cases do not overcome the insufficiencies of the disclosure.

Applicant argues (page 13) that the PRO300 gene can be used to differentiate tumor from normal tissue and the fact that the types of lung tumors which were assayed were not described does not detract from Applicant's asserted utility. However, in the instant case, PRO300 mRNA was found to be in greater abundance in normal tissue compared to "lung tumor". However, the lack of information regarding types of tumors weighs heavily on the enablement of the claimed invention. It is known in the art that cancers from a common tissue (i.e. lung) have different gene expression patterns, which is why different chemotherapeutic therapies are required for different forms of cancer. Therefore, it would be reasonable to conclude that depending on what type of "lung tumor" tissue was used for the comparison in Example 18, the data could be skewed for a false positive or false negative result. If the gene is not expressed in stage 3 adenocarcinomas of the lung, but is expressed in stage 1 adenocarcinomas of the lung and the "lung tumor" tissue used in Example 18 was only from stage 3

adenocarcinomas, one of ordinary skill in the art would not be able to make a correct diagnosis of lung tumor for a stage 1 adenocarcinoma of the lung because it would be a false negative result. Therefore, the lack of information as to what types of tissues were used in Example 18 is quite relevant to utility and enablement because a person in the art at the time of the instant invention would be required to perform additional experimentation to reasonably confirm a use in detection of lung tumor for the reasons given in this and previous Office actions.

Applicant argues (page 14) that the "Examiner has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Girmaldi based his opinion". Applicant's argument has been considered, but has not been found to be persuasive. Several pages of reasons and explanation were provided in the previous Office actions, as well as supporting references from peer-reviewed journals to support the underlying rationale of the reasons and explanation. The fact that Mr. Grimaldi's Declaration was not found persuasive is not evidence that it was "summarily dismissed" and Applicant is reminded that when conclusions are made with no supporting evidence, then such statements are viewed as opinions which can be rebutted with evidence. Such has been the case in the instant application.

Applicant argues (page 15) that Example 18 provides evidence that there is a two-fold difference in cDNA between tumor tissue and normal tissue and that the results are reliable enough that they can be used to distinguish tumor from normal. The argument has been fully considered, but is not persuasive. Further, for the instant claims, the encoded protein must have diagnostic utility since the

claims are directed to antibodies that bind the protein. For reasons discussed here and in the previous Office action, it is maintained that the protein, and likewise, the antibody that binds it, does not have such utility.

Applicant argues (pages 15-17) that the declarations of Grimaldi and Polakis support the teachings in Molecular Biology of the Cell, Genes VI, and Zhingang et al. (2004), that it is generally accepted that mRNA and protein expression are positively correlated. The argument has been fully considered, but is not persuasive. As discussed above, there is sound supporting evidence showing the unpredictability of saying level of expression of a particular nucleic acid will correlate with expression of the encoded protein. The argument of correlation between nucleic acid and protein expression has been previously addressed. Zhighan find that a correlation between mRNA and protein expression for the PSCA nucleic acid examined occurred in 93% of the samples so that it may be a promising diagnostic marker. There is no requirement for utility that a 100% correlation be present. Nevertheless, in the instance application, we have no correlation. There is no suggestion of multiple tumors tested. There are only just "cDNA libraries isolated from different human tumor and normal human tissue samples." The declaration of Grimaldi says these samples were pooled samples. No relative or absolute values of expression for protein or nucleic acid were given in the specification. As discussed above, it is not clear whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested for the PRO300 nucleic acid and/or protein. If Zhinghan et al. had obtained only a 5% correlation, it is doubtful he would have concluded that

the nucleic acid would be a promising molecular marker.

Applicants argue the Meric et al. (Mol. Cancer Ther., 2002) says that cancer therapeutics relies on exploiting differences in gene expression between cancer and normal cells. While this statement is generally true, the instantly claimed invention cannot be used as a cancer therapeutic or diagnostic because of the information missing to support such a use as discussed above.

Applicant argues (page 18) that a lack of known role for PRO300 in cancer does not prevent its use as a diagnostic tool for cancer. The argument has been fully considered, but is not persuasive. It is correct that the role of a gene need not be known, but the specification and/or prior art needs to enable that particular gene to be used diagnostically regardless of function. Further, for the instant claims are directed to antibodies and not the gene; therefore, the encoded protein must have diagnostic utility for the antibodies to have diagnostic utility. Fore reasons discussed here and in the previous Office action, it is maintained that the protein does not have such utility. Applicant makes note that the PTO has issued several patents claiming differentially expressed polypeptides. Applicant is reminded that the instant specification has no evidence that the encoded protein of PRO300 demonstrates differential expression.

Applicant argues (pages 19-20) that the results of Hu et al. (J. Proteome Res., 2003) are not surprising and provide little if any information about genes with less than 5-fold differential expression in tumor compared to normal tissue. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a

correlation between expression level and activity. The caution provided in the last paragraph of page 411 is noteworthy. "It is not uncommon to see expression changes in micro array experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful." As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are significant.

Applicant argues (pages 20-21) that the results of Gygi et al. would support a general correlation between mRNA and protein levels. This argument has been fully considered, but is not persuasive. The Examiner did not conclude anything related to the correlation of transcript levels to protein expression. Rather, Gygi et al. concluded that transcript levels provide little predictive value with respect to the extent of protein expression (see page 1730, column 1, final sentence). It was pointed out that there was a general trend of increased protein levels resulting from increased mRNA levels, but Gygi et al. state that this number was highly biased by a small number of genes with very large protein and message levels (see page 1726, column 1, paragraph 2). For genes with low message levels (69% of the genes studied), the correlation coefficient was only .356, demonstrating that message levels are generally not predictive of protein levels for the majority of the genes studies by Gygi et al. Applicant has not demonstrated that the gene of the instant application is one with high message levels, therefore, no assumptions can be made regarding protein expression. Based on the teachings of Gygi et al., it would be reasonable to

conclude that transcript levels provide little predictive value with respect to protein expression and no meaningful information regarding protein expression can be gleaned from the data presented in Example 18.

Applicant concludes (pages 22-23) that the claimed invention has a specific utility as a cancer diagnostic tool, particular for lung tumors. The argument has been fully considered, but is not persuasive. The reasons for this have been discussed at length above, but include relative or absolute levels of the difference(s) in PRO300 protein level in tumor *vs.* normal lung tissue are not provided, the lack of information about particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), the lack of information about repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and the unpredictability of correlation mRNA and protein expression levels. For these reasons, it is maintained that there is no substantial and specific utility for the antibodies that bind the polypeptide of SEQ ID NO:12.

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for the reasons of record.

Applicant asserts that the arguments regarding the utility of the claimed invention are sufficient to overcome the enablement rejection of the claims under 35 U.S.C. 112. However, since the submitted arguments were not persuasive to

overcome the utility rejections under 35 U.S.C. 101, they are also not persuasive to overcome the instant rejection.

It would require significant further experimentation to be able to use the claimed antibodies because no definite function has been determined for the encoded protein, there is no definite function supported by the prior art, and there has been no correlation provided between the protein and any disease state. The specification does not provide sufficient guidance or working examples to be able to use the encoded polypeptide nor the antibodies that bind it diagnostically or therapeutically, for example in association lung tumors, without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are directed to an antibody that specifically binds to the protein of SEQ ID NO:12. However, it is not clear how the limitation "specifically" is to be interpreted. It is not clear if there is a basis in the instant specification as filed and antibodies bind to proteins specifically in that they bind to antigenic portions of the proteins. An antibody will bind the amino acids of the antigenic portion in whatever protein the sequence is located. Therefore, it is not clear what the metes and bounds of the term "specifically" are and in the event that

Applicant intends this language to mean that the antibody binds the recited protein and no other protein, a new ground of rejection for lack of enablement and/or written description may be required.

35 U.S.C. § 102

The following rejections under 35 U.S.C. § 102 is made under the assumption that the effective filing date for the instantly claimed invention is 05/07/2002, which is the actual filing date of the instant application. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. §120 from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the new claimed invention. Because the instant application does *not* meet the requirements of 35 U.S.C. § 112, first paragraph, for the reasons given above and it is a continuing application of Serial Number 10/006,867, the prior application also does not meet those requirements for the claimed invention and, therefore, is unavailable under 35 U.S.C. § 120.

Claim Rejections - 35 USC § 102

Claims 1-5 stand rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/16318 for the reasons of record in the previous Office action.

Applicant argues (page 24) that they have made a proper claim of priority under 120 to obtain benefit of the WO 01/16318. However, benefit under 120

requires fulfillment of the requirements of 112, which includes a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. Since the instant specification does not meet the requirements of 35 U.S.C. 112, the instant application does not obtain benefit of the earlier filed application. Since the earlier filed application was published more than 1 year before filing the instant application, it is proper art under 102(b).

Applicant argues that the data in Example 18 was first disclosed in PCT application PCT/US00/23328, and therefore, priority benefit should date back to this application. However, because of the reasons of record, the data in this example does not provide a specific, substantial and credible utility for the claimed invention, and therefore, the requirements of 35 U.S.C. 112, first paragraph are not met and benefit is not granted.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on mttr, 8:00-2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CHRISTINE J. SAOUD
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Christine Saoud